

REMARKS

In response to the advisory action mailed on October 20, 2008 (“Advisory Action”) and the final office action mailed on July 10, 2008 (“Office Action”), Applicants submit the following remarks. Claims 1, 3-15, 17-27, 29-33, and 35-37 are pending. No claim amendments are presented.

Rejections Under 35 U.S.C. 103(a)

For at least the reasons below, the prior art does not disclose or render obvious the claimed invention.

Rejection under 35 U.S.C. §103(a) over Smith/Gray/Kaminski

Claims 1, 3-10, 15, 17-27, 29-31 and 35-37 stand rejected for allegedly being obvious over a combination of US 5,888,930 (“SMITH”), PCT/AU01/01370 published as WO02/34300 (“GRAY”) and US 6,015,542 (“KAMINSKI”). The Examiner maintains that it would have been obvious to modify the teachings of SMITH to provide a cross-linked particle based on GRAY in combination with a radioisotope based on GRAY and KAMINSKI (Office Action at pages 3-5 and Advisory Action at page 2). Applicant respectfully argues that (1) the Examiner has failed to make a *prima facie* case for this rejection in both the Office Action and the Advisory Action and (2) the asserted combination of references do not disclose or render obvious the claimed invention.

Claims 1 and 3-10 cover compositions including a particle having a cross-linked polymer matrix. The particles also have a first region including pores with a first predominant pore size and a second region surrounding the first region, where the second region has pores having a second predominant pore size and the first predominant pore size is larger than the second predominant pore size. Claims 15 and 17-26 recite methods of delivering a composition including such a particle and claims 27-31 and 35-37 recite methods of manufacturing such particles.

First, Applicant respectfully submits that the Examiner has failed to meet the standard to establish *prima facie* obviousness of the claimed particles and methods by suggesting

modifications of the SMITH reference based on mere conclusory statements from GRAY without any demonstrated basis in the prior art for such modifications. The standard for *prima facie* obviousness is clear in the case law, as described in the MPEP §2142 and elsewhere:

[t]he legal concept of *prima facie* obviousness... allocates who has the burden of going forward with production of evidence in each step of the examination process... The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness (MPEP 2142, citations omitted).

As further noted in the MPEP, the Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." (MPEP §2142, citing *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) and *KSR Int'l v. Teleflex, Inc.*, 127 S.Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007) (quoting Federal Circuit statement with approval)).

In this case, the Examiner has failed to articulate adequate support for the proposed modification of SMITH to disclose the limitations of the rejected claims. As recited in the Office Action, SMITH "fails to include the polymeric matrix compris[ing] a cross-linked polymer" (Office Action at page 3). The Office Action merely states that "it is noted that Gray teaches that it is preferred that the polymeric matrix is partially cross-linked" (Office Action at page 4) to support a modification of SMITH to include polymer cross-linking in a particle comprising the pore size regions as claimed. The portion of GRAY cited in support of this statement merely states that "[i]n a preferred embodiment the polymeric matrix is partially cross linked" (GRAY, page 6, line 8). GRAY does not describe how such cross-linked polymer matrices are made, nor provide any guidance how the beads or bead-forming methods of SMITH may be modified to achieve the cross-linked polymer particles recited in the rejected claims. The Advisory Action asserts that modification of SMITH to obtain the claimed particle compositions and methods would be within the skill of one of ordinary skill in the art, without articulating any basis in the prior art for such a modification:

[t]o respond, it is noted that after reviewing the solvents and the rules of using the solvents as disclosed in Smith is a conventional chemical instruction that have never stopped people having skill in the art from modifying different disclosures (Advisory Action at page 2, lines 5-6).

Both the Examiner's citation to GRAY in the Office Action and the Examiner's characterization of SMITH in the Advisory Action as a "conventional chemical instruction" that may be "modified" without basis in cited prior art fail to meet the applicable *prima facie* standard for an obviousness rejection.¹ Such statements that modifications of the prior art to meet the claimed invention would have been within the ordinary skill of the art at the time the claimed invention was made because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references (MPEP §2142, citations omitted, emphasis added). The Examiner's recitation of a combination of GRAY (reciting cross-linked particles without specifying the pore structure), SMITH (reciting a pore structure without cross-linking) and KAMINSKI (unrelated to the formation or use of porous beads or particles) do not together amount to a *prima facie* case of obviousness by the Examiner. The disparate existence in the art of some aspects of the claimed invention is not sufficient to establish a *prima facie* case of obviousness. Reconsideration and withdrawal of this rejection is requested at least on this basis.

Secondly, the SMITH, GRAY and KAMINSKI references (either individually or any combination thereof) do not disclose or render obvious particles having both a cross-linked polymer matrix and multiple regions of different pore sizes, or methods of making such particles. SMITH is not, as the Advisory Action asserts, "a conventional chemical instruction" that may be "modified" based on the skill in the art or the teachings of GRAY to obtain the cross-linked porous particles and methods claimed (Advisory Action at p. 2). To the contrary, SMITH describes beads with "a unique, continuously-gradated asymmetric microporous structure"

¹ Nor does combination with KAMINSKI provide a *prima facie* argument on the part of the Examiner. The Advisory Action acknowledges that KAMINSKI "was relied upon for teaching the radioactively labeled monoclonal antibody or radioactively labeled monoclonal antibody which binds to the antibody on the surface of cells (claim 1) and which can be labeled with a radioisotope (example III) to treat cancers," rather than to teach cross-linking of the porous beads of SMITH (Advisory Action at page 2).

(SMITH at col. 2, lines 50-52). SMITH describes *very specific* methods of preparing such non-crosslinked porous beads by precipitation of a polymer (e.g., SMITH at col. 3, lines 10, 22, 39, 46 and 51 and col. 5, line 19) where:

[t]he key to achieving the characteristic continuously-gradated asymmetric pore structure of the beads of the present invention is keeping the rate of solvent exchange with the liquid of the precipitation bath slow following a rapid initial precipitation that forms the "skin" layer (SMITH at col. 3, lines 6-10).

In SMITH, porous beads are formed by precipitation methods that require very particular combinations of solvents and polymers. SMITH discloses formation of porous beads either (1) by solvent exchange when a polymer-solvent solution is contacted with a liquid miscible with the solvent (but not the polymer), leading to exchange of the solvent into the liquid and precipitation of the polymer to form the porous particle (e.g., SMITH at col. 3, lines 6-67), or (2) by evaporation of a volatile solvent (e.g., SMITH at col. 5, lines 13-27) with mid-air precipitation of the polymer. SMITH teaches that only a very limited and specific number of solvent-polymer-liquid combinations can be used in the manner provided to obtain precipitated porous beads:

[i]n order to achieve the continuously-gradated pore structure of the beads of the present invention, the polymer, its solvent and the precipitation bath must all be specified (SMITH at col. 3, lines 49-51, emphasis provided).

In fact, SMITH contains numerous restrictions on the polymers, solvents and nonsolvent liquid combinations that may be used to form porous microbeads, but fails to provide any mention of how the method may be modified to provide a crosslinked porous bead. For example, according to SMITH, the solvent "must dissolve the polymer and be miscible with the liquid, typically water, used for precipitation" (SMITH at col. 3, lines 3-5); the polymer "must be soluble in a suitable solvent and insoluble in a liquid that is miscible with the solvent (SMITH at col. 2, line 67 – col. 3, line 1); the rate of solvent exchange with the liquid must be kept slow following a rapid initial precipitation (SMITH at col. 3, lines 8-10); and the polymer solution may only contain a liquid nonsolvent in amounts "that the polymer does not begin to precipitate, but remains completely dissolved" (SMITH at col. 4, lines 38-42).

There is no basis in the level of skill in the art or the GRAY reference to modify the narrow bead-forming compositions and/or conditions taught in SMITH to produce a cross-linked porous particle as claimed. The bead-forming process of SMITH is highly sensitive to the bead-forming composition and conditions, to such an extent that SMITH teaches away from modifications of these specific bead-forming compositions and conditions. The pore structure of the beads in SMITH is highly dependent on the combination of solvent, polymer and non-solvent liquid (e.g., SMITH at col. 3, lines 50-51). The manner in which SMITH cautions against modifications of the bead-forming composition and conditions teaches away from modifications, such as modifications aimed at the formation of cross-links in the porous beads.

Nor does combination of SMITH with GRAY disclose or render obvious the claimed compositions and methods. GRAY merely discloses the use of cross-linked particles with a radionuclide, without any mention of the pore size distribution within the particles (See, e.g., GRAY, p. 6, lines 11-17; p. 7, lines 13-17; p. 9, lines 7-12). In particular, GRAY recites only the selection and use of "partially cross linked" polymer matrices in a "particulate material" (GRAY at p. 6, lines 8-17). GRAY does not disclose either the selection or use of polymer matrices having regions of varying predominant pore sizes, nor how to modify a precipitation method of SMITH to obtain cross-linked beads. GRAY does not even disclose how to make his particle, let alone how to modify it such that it would have the pore structure required by claims 1, 3-10, 15, 17-27, 29-31 and 35-37. Nothing in GRAY discloses how to modify the bead-forming compositions and conditions of SMITH to obtain the claimed particles and methods. Nor does GRAY itself describe how to form cross-linked particles with a region having pores of a larger predominant pore size than pores in another region.

KAMINSKI does not cure the deficiencies of SMITH, GRAY or the combination of SMITH and GRAY. KAMINSKI describes radioactively labelled B1 antibodies "which bind specifically to the CD20 antigen of B cells" and related "methods for immunotherapy of lymphoma which employ the B1 antibody (KAMINSKI, at col. 5, lines 21-25). KAMINSKI does not disclose the manufacture or use of porous particles or beads. Nothing in KAMINSKI describes or renders obvious the modification of the bead-forming compositions and methods of SMITH. As the Advisory Action states, KAMINSKI "was relied upon for teaching the radioactively labeled

monoclonal antibody or radioactively labeled monoclonal antibody...," rather than cross-linking of porous particles or beads (Advisory Action at page 2).

Third, the SMITH, GRAY and/or KAMINSKI references, alone or in combination, do not enable the claimed particles and methods relating to a cross-linked polymer matrix and regions of different predominant pore sizes. Applicable caselaw clearly states that "[i]n order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." *Beakman Instruments, Inc. v. LKB Produkter AB*, 892 F2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989). A claim rejection for obviousness under 35 USC 103 is improper if the person of ordinary skill in the art would not be able to make a claimed composition or perform a claimed method upon reviewing the cited prior art without undue experimentation:

[r]eferences relied upon to support a rejection under 35 USC 103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public. [citations omitted] An invention is not 'possessed' absent some known or obvious way to make it." *In re Payne, Durden and Weiden*, 606 F2d 303, 314, 203 USPQ 245, 255 (CCPA 1979).

Under this standard, an obviousness rejection under 35 USC 103 of a composition claim is improper in "the absence of a known or obvious process for making the claimed compounds." *In re Hoeksema*, 399 F2d 209, 274, 158 USPQ 596, 601 (CCPA 1968).

In this case, the obviousness rejection based on SMITH, GRAY and/or KAMINSKI is improper under this applicable legal standard because the Examiner provides no basis to actually make the claimed cross-linked porous particles. Given the highly detailed restrictions on bead-forming compositions and conditions in SMITH discussed above (e.g., SMITH at col. 2, line 67 – col. 3, line 67), and the sensitivity of the precipitation mechanism disclosed SMITH to these parameters (e.g., SMITH at col. 3, lines 6-16), one skilled in the art would not modify the compositions and methods of SMITH with any reasonable expectation of obtaining a the cross-linked porous particles as claimed. Accordingly, neither SMITH nor GRAY, alone or in combination, disclose or render obvious the claimed particle compositions and methods.

Thus, after reading SMITH, it not only would not have been obvious to one of ordinary skill in the art to modify SMITH's process to provide the particles covered by claims 1, 3-10, 15, 17-

27, 29-31 and 35-37, one skilled in the art would not have even wanted to try to modify Smith's process. Even if one skilled in the art had somehow tried to modify SMITH to provide the particles covered by these claims, SMITH would not have enabled a person to do so as Smith clearly does not disclose how to make such a particle with a cross-linked particle, let alone such a particle with the pore properties required by claims 1, 3-10, 15, 17-27, 29-31 and 35-37.

For at least these reasons, Applicants request reconsideration and withdrawal of this rejection.

Rejection under 35 U.S.C. §103(a) over Smith/Gray/Ajay

The Examiner rejected claims 11-12 under 35 U.S.C. §103(a) as being unpatentable over SMITH in view of GRAY and the publication by Ajay K. et al., "Extended preoperative polyvinyl alcohol microembolization of intracranial meningiomas: assessment of two embolization techniques," AJNR 14, 571-582 (1993) ("AJAY"). For at least the reasons discussed above, neither SMITH nor GRAY, alone or in combination, discloses or renders obvious the particle compositions of claims 11 and 12. The asserted combination of SMITH and GRAY with AJAY do not address the shortcomings of SMITH and GRAY, or a combination thereof for at least two reasons.

First, the Examiner fails to provide a *prima facie* basis for the assertion that the combination with AJAY with SMITH and/or GRAY renders the claimed compositions obvious. The Office Action asserts that "it would have been obvious... to use polyvinyl particles as a carrier for a radioisotope which may be attached to an antibody... and apply it to the anisotropic pore structure of Smith" (Office Action at page 5). Applicants respectfully disagree. AJAY is a medical journal article describing tumor embolization using non-porous 50-150 or 150-300 micrometer polyvinyl alcohol (PVA) polymer particles. AJAY describes injection of PVA particles with an "irregular surface" and a "high coefficient of friction" to provide microembolization of intracranial meningiomas (e.g., AJAY at pages 580-581). The Examiner has not provided any basis in AJAY to modify the bead-forming compositions of SMITH or the combined teachings of SMITH and GRAY to obtain the claimed compositions or methods. The Examiner's recitation of a combination of GRAY (reciting cross-linked particles without specifying the pore structure), SMITH (reciting a pore structure without cross-linking) and AJAY

(a reference completely silent on both pore structure and cross-linking) do not together amount to a *prima facie* case of obviousness by the Examiner. The disparate existence in the art of some aspects of the claimed invention is not sufficient to establish a *prima facie* case of obviousness (See, e.g., MPEP §2142).

Second, AJAY does not render the claimed compositions and methods obvious alone or in combination with SMITH and/or GRAY. The combination of SMITH and GRAY do not teach or render obvious the claimed porous particles having a cross-linked polymer matrix for at least the reasons described above. Neither AJAY nor the combination of AJAY and GRAY provide any guidance on how to modify the bead-forming compositions and methods of SMITH. AJAY does not disclose or even relate to the manufacture or use of porous particles, such as those described in SMITH. In fact, the porous beads disclosed in SMITH may reduce the coefficient of friction of the outside surface of the bead or even permit fluid to leak around or through the particles, contrary to the treatment objectives in AJAY. Furthermore, like the discussion of GRAY above, AJAY is similarly silent on how to form such polymer particles, or how to modify the teachings of SMITH to obtain cross-linked porous beads.

Third, the SMITH, GRAY and/or AJAY references, alone or in combination, do not enable the claimed particles and methods relating to a cross-linked polymer matrix and regions of different predominant pore sizes. The obviousness rejection based on SMITH, GRAY and/or AJAY is improper under the applicable legal standard discussed above because the Examiner provides no basis to actually make the claimed cross-linked porous particles. For at least these reasons, neither AJAY alone, nor AJAY in combination with SMITH and/or GRAY, enable one skilled in the art to modify SMITH's bead-forming compositions and methods to provide the particles described by claims 11-12. Accordingly, the asserted combination of SMITH, GRAY and AJAY, alone or in any combination, do not disclose or render obvious the particles covered by claims 11-12.

For at least these reasons, Applicants request reconsideration and withdrawal of this rejection.

Rejection under 35 U.S.C. §103(a) over Smith/Gray/Atcher

The Examiner rejected claims 13-14 and 32 under 35 U.S.C. §103(a) as being unpatentable over SMITH and GRAY in view of Atcher et al., US 4,970,062 (“ATCHER”). For at least the reasons discussed above, neither SMITH nor GRAY, alone or in combination, discloses or renders obvious the particle compositions of claims 13-14 and 32. The asserted combination of SMITH and GRAY with ATCHER do not address the shortcomings of SMITH and GRAY, or a combination thereof for at least two reasons.

First, the Examiner fails to provide a *prima facie* basis for the assertion that the combination with ATCHER with SMITH and/or GRAY renders the claimed compositions obvious. The Office Action asserts that “it would have been obvious... to develop a particle made of a polymer in an anisotropic pore structure like Smith's and attach the radionuclide because Atcher that the surface attached radionuclides can be used in cancer therapy” (Office Action at page 6). Applicants respectfully disagree. The colloid particles disclosed in ATCHER are not formed from a polymer, and are not porous. Instead, ATCHER provides a radioactive ferric hydroxide colloid with a radionuclide “essentially only on the outer surfaces” of the colloid (e.g., ATCHER at col. 3, lines 25-47), such as a ferric hydroxide colloid having radioactive ²¹²Pb on the outer surface of the colloid (col. 3, lines 62-65). The Examiner has not provided any basis in ATCHER to modify the non-crosslinked polymer bead-forming compositions of SMITH or the combined teachings of SMITH and GRAY to obtain the claimed compositions or methods. The Examiner's recitation of a combination of GRAY (reciting cross-linked particles without specifying the pore structure), SMITH (reciting a pore structure without cross-linking) and now ATCHER (a reference relating to non-polymeric and non-cross-linked inorganic compositions) do not together amount to a *prima facie* case of obviousness by the Examiner. The disparate existence in the art of some aspects of the claimed invention is not sufficient to establish a *prima facie* case of obviousness (See, e.g., MPEP §2142).

Second, ATCHER does not render the claimed compositions and methods obvious alone or in combination with SMITH and/or GRAY. The combination of SMITH and GRAY do not teach or render obvious the claimed porous particles having across-linked polymer matrix for at least the reasons described above. Neither ATCHER nor the combination of ATCHER with SMITH and/or GRAY provide any guidance on how to modify the bead-forming compositions

and methods of SMITH to provide the cross-linked porous particles recited in the rejected claims. ATCHER does not disclose or even relate to the manufacture or use of porous particles, such as those described in SMITH. ATCHER describes the preparation of radioactive ferrous hydroxide, a non-porous and non-polymer composition having a radionuclide (e.g., 212Pb) on the outer surface of the ferrous salt (ATCHER at col. 3, lines 29-35 and 48-68). ATCHER describes the in vivo therapeutic effect of injecting these radioactive colloid compositions against the Ehrlich ascites carcinoma model in mice (ATCHER at col. 4, lines 1-17). However, like the discussion of GRAY above, ATCHER is completely silent on how to form cross-linked porous polymer particles, or how to modify the teachings of SMITH to obtain the claimed compositions. ATCHER does not enable one skilled in the art to modify SMITH's bead-forming compositions and methods to provide the particles described by claims 11-12. Accordingly, the asserted combination of SMITH, GRAY and AJAY, alone or in any combination, do not disclose or render obvious the particles covered by claims 13-14 and 32.

Third, the SMITH, GRAY and/or ATCHER references, alone or in combination, do not enable the claimed particles and methods relating to a cross-linked polymer matrix and regions of different predominant pore sizes. The obviousness rejection based on SMITH, GRAY and/or ATCHER is improper under the applicable legal standard discussed above because the Examiner provides no basis to actually make the claimed cross-linked porous particles. For at least these reasons, neither ATCHER alone, nor ATCHER in combination with SMITH and/or GRAY, enable one skilled in the art to modify SMITH's bead-forming compositions and methods to provide the particles described by claims 13-14 and 32. Accordingly, the asserted combination of SMITH, GRAY and ATCHER, alone or in any combination, do not disclose or render obvious the particles covered by claims 13-14 and 32.

For at least these reasons, Applicants request reconsideration and withdrawal of this rejection.

Double Patenting

The Examiner rejected claims 1, 3-15, 17-27, 29-33, and 35-37 on the ground of nonstatutory obviousness-type double patenting, citing eight commonly owned patent

applications. In view of the other rejections to claims 1, 3-15, 17-27, 29-33, and 35-37, Applicants request that these rejections be held in abeyance.

Conclusion

For at least the reasons outlined herein, as well as reasons articulated in Remarks submitted in the AMENDMENT IN REPLY TO ACTION OF JANUARY 25, 2008, submitted April 15, 2008 (incorporated herein by reference), Applicants request reconsideration and withdrawal of these rejections.

Applicants believe that the claims are in condition for allowance, which action is requested.

Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 01194-458001.

Respectfully submitted,

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